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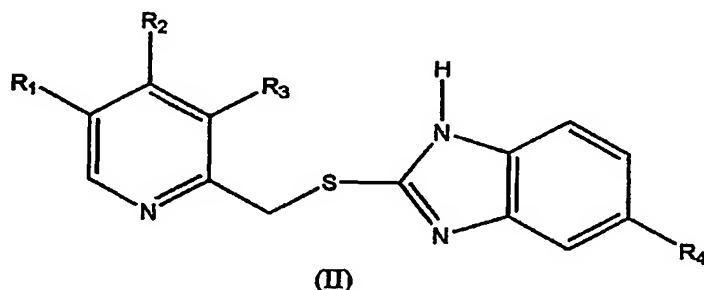
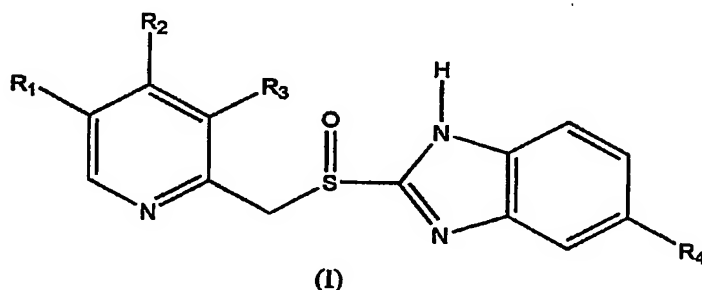
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[Continued on next page]

(54) Title: **PAHARMACEUTICAL PROCESS AND COMPOUNDS PREPARED THEREBY**



(57) Abstract: The present invention relates to an improved process for the preparation of a sulfinyl compound of formula (I), or a pharmaceutically acceptable salt, hydrate or solvate thereof, from a sulfide compound of formula (II), wherein in both formulae (I) and (II) R₁ and R₃ are selected from the group consisting of hydrogen, methyl or C₁₋₄alkoxy, R₂ is selected from the group consisting of substituted or unsubstituted C₁₋₄alkoxy and R₄ is selected from the group consisting of hydrogen or substituted or unsubstituted C₁₋₄alkoxy.



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PHARMACEUTICAL PROCESS AND COMPOUNDS PREPARED THEREBY

The present invention relates to an improved process for preparation of proton pump inhibitors, and to such proton pump inhibitors prepared thereby, compositions containing the same and uses thereof.

Gastric proton pump inhibitors (PPIs) include substituted 2-(2-pyridylmethyl)-sulfinyl-1H-benzimidazoles, such as lansoprazole (2-[[[3-methyl-4-(2,2,2-trifluoro-ethoxy)-2-pyridinyl]methyl]sulfinyl]1H-benzimidazole), omeprazole (5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole), pantoprazole (5-(difluoromethoxy)-2-[[[3,4-dimethoxy-2-pyridinyl]methyl]sulfinyl]1H-benzimidazole) and rabeprazole (2-[[[4-(3-methoxy-propoxy)3-methyl-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole). These compounds can produce profound and sustained inhibition of gastric acid secretion, with responses of PPIs being more rapid compared with those seen with other anti-secretory drugs. PPIs work by inhibiting the production of stomach acid, by shutting down a system in the stomach known as proton pump, the full name of which is the hydrogen-potassium adenosine triphosphate enzyme system. PPIs are the drugs of choice in dyspepsia and peptic ulcers, and also Zollinger-Ellyson syndrome. In particular, in the treatment of peptic ulcers, the response rates of PPIs are superior to those seen with other drugs.

The reported prior art synthesis of these substituted 2-(2-pyridylmethyl)-sulfinyl-1H-benzimidazoles generally involves an oxidation process of a sulfide compound to the corresponding sulfinyl compound. More particularly, prior art processes for the preparation of 2-(2-pyridylmethyl)-sulfinyl-1H-benzimidazoles, generally involve the synthesis of the corresponding thioether compound, and its subsequent oxidation to the sulfinyl or sulfoxy compound, by various methods such as reaction with hydrogen peroxide over a vanadium compound catalyst, or reaction with peracids, peresters or ozone. There are several disadvantages associated with such known processes, primarily with respect to the nature of the thioether (or sulfide) compound being oxidized.

US Patent No. 4,628,098 to Nohara, et al. discloses a process for preparation of lansoprazole by oxidation of the sulphide precursor compound using peracids (m-chloro perbenzoic acid).

US Patent No. 5,840,552 to Holt, et al. discloses a process for preparation of lansoprazole, wherein the sulphide precursor compound was selectively bio-oxidised to isolate the pharmaceutically active enantiomer or enantiomerically enriched corresponding sulfoxide form, using microorganisms or a microbial enzyme system.

US Patent No. 5,374,730, to Slemon, et al. discloses a process for the preparation of omeprazole and lansoprazole, wherein amide analogues of the thioether compounds were readily oxidized to the corresponding sulfinyl compounds and the sulfinyl compounds were hydrolyzed in an alkaline medium to the corresponding carboxylic acid salts. The salts were subsequently decarboxylated to omeprazole or lansoprazole respectively. The disclosure refers to the advantages in relation to the purity of the final products, and the simplicity of the purification procedures. The amide compounds which were subjected to the oxidation step were crystalline solids, as opposed to oils, and as such could be readily purified to a high degree of purity by relatively simple precipitation, crystallization and washing procedures. The carboxylates and carboxylic acid salts which were formed in the subsequent synthetic step after oxidation were water soluble, whereas the final products, omeprazole and lansoprazole, are not water soluble. Accordingly, any un-reacted residues, and also other minor impurities in the final products, were simply removable by an aqueous washing procedure. Avoidance of significant discoloration of the product was the other advantage disclosed.

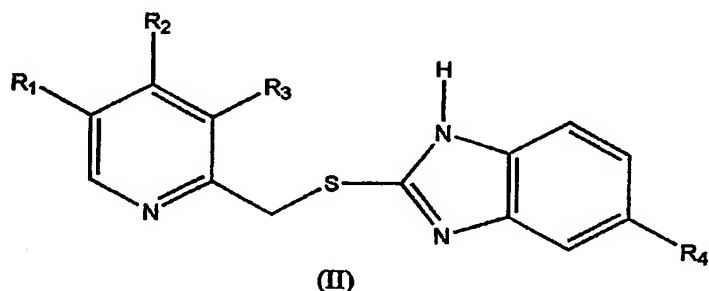
US Patent No. 5,470,983 to Slemon, et al. discloses processes for producing lansoprazole from acetamide-sulfide compounds by a process of oxidation to form the amide sulfinyl compound, followed by alkaline hydrolysis to the sulfinyl carboxylate or salt, and decarboxylation.

US Patent No. 5,502,195, to Slemon, et al. discloses a process for preparation of lansoprazole, wherein the acetamide sulphide was oxidized to the corresponding amide sulfinyl compound, which was subsequently hydrolysed in an alkaline medium to the carboxylic acid salt and then decarboxylated to form lansoprazole.

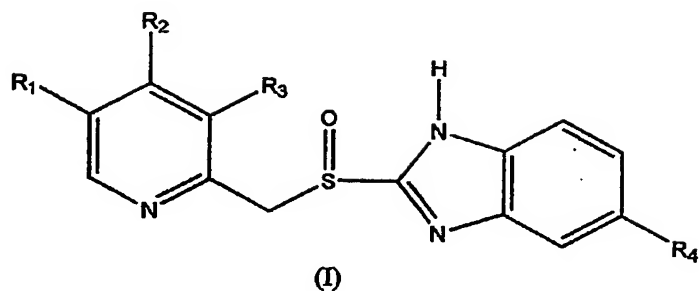
US Patent No. 6,423,846 to Moon, et al. discusses problems associated with prior art oxidation procedures for converting precursor compounds into lansoprazole, where many by products were formed and the yield of lansoprazole was low. EP Patent No. 134,400, GB Patent No. 2,134,523, US Patent No. 4,628,098 and Korean Patent No. 52,837 each disclose m-chloroperbenzoic acid as the oxidant. Spanish Patent Nos. 550,057; 540,147 and 539,793 respectively disclose sodium periodate, iodosomethylbenzene and iodosobenzene as the oxidant employed. These prior art processes were cited as being unviable because of the expensive oxidants used therein, the formation of many impurities and a low yield of the product in the range of about 60 to 80%.

All these prior art process either use expensive catalysts or hazardous oxidizing reagents, such as peracids, which are not suitable for commercial manufacture of these compounds. Also over-oxidation of the thioether compound to the corresponding sulphone analogue is a common problem encountered with the prior art processes.

There has thus been a long felt need for efficient and safe methods for the selective oxidation of a sulphide compound of formula (II)



to a sulfinyl compound of formula (I)



wherein in both formulae (I) and (II) R_1 and R_3 are selected from the group consisting of hydrogen, methyl or C_{1-4} alkoxy, R_2 is selected from the group consisting of substituted or unsubstituted C_{1-4} alkoxy and R_4 is selected from the group consisting of hydrogen or substituted or unsubstituted C_{1-4} alkoxy.

The present invention now provides an efficient, safe and industrially feasible method for preparing various substituted 2-(2-pyridylmethyl)-sulfinyl-1H-benzimidazoles.

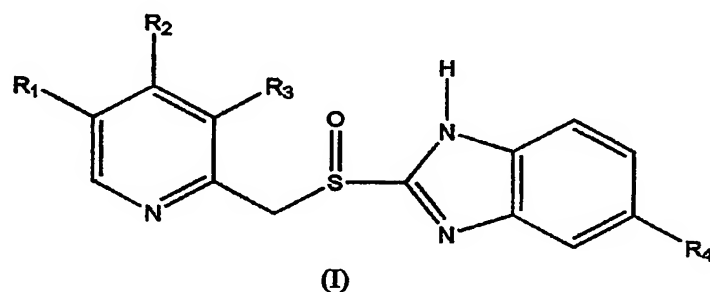
In particular, it is an aim of the present invention to provide an improved process for oxidation of (2-[[[3-methyl-4-(2,2,2-trifluoro-ethoxy)-2-pyridinyl]methyl]thio]1H-benzimidazole to the corresponding (2-[[[3-methyl-4-(2,2,2-trifluoro-ethoxy)-2-pyridinyl]methyl]-sulfinyl]1H-benzimidazole (lansoprazole), preferably using an eco-friendly, inexpensive and readily available reagent.

It is a further aim of the present invention is to provide an improved process for oxidation of ((5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridyl]methyl]-thio]-1H-benzimidazole, to the corresponding ((5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridyl]methyl]-sulfinyl]-1H-benzimidazole (omeprazole), preferably using an eco-friendly, inexpensive and readily available reagent.

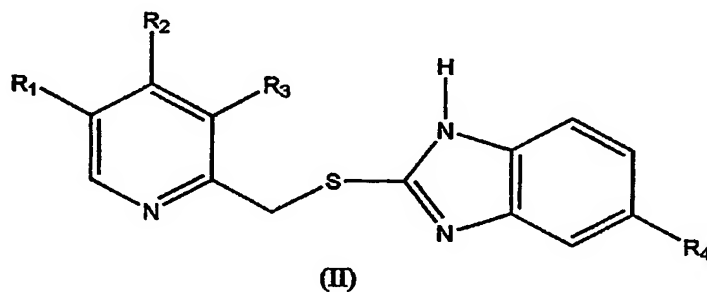
It is a further aim of the present invention is to provide an improved process for oxidation of ((5-(difluoromethoxy)-2-[[[3,4-dimethoxy-2-pyridinyl]methyl]thio]1H-benzimidazole, to the corresponding ((5-(difluoromethoxy)-2-[[[3,4-dimethoxy-2-pyridinyl]methyl]-sulfinyl]1H-benzimidazole (pantoprazole), preferably using an eco-friendly, inexpensive and readily available reagent.

It is a still further aim of the present invention is to provide an improved process for oxidation of (2-[[[4-(3-methoxy-propoxy)3-methyl-2-pyridinyl]methyl]-thio]-1H-benzimidazole, to the corresponding (2-[[[4-(3-methoxy-propoxy)3-methyl-2-pyridinyl]methyl]-sulfinyl]-1H-benzimidazole (rabeprazole), preferably using an eco-friendly, inexpensive and readily available reagent.

More particularly, the present invention provides a process for preparing a sulfinyl compound of formula (I), or a pharmaceutically acceptable salt, hydrate or solvate thereof,



which process comprises oxidation of a sulfide compound of formula (II)



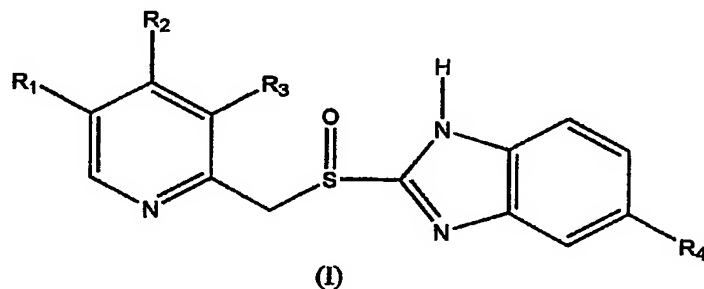
wherein in both formulae (I) and (II) R_1 and R_3 are selected from the group consisting of hydrogen, methyl or C_{1-4} alkoxy, R_2 is selected from the group consisting of substituted or unsubstituted C_{1-4} alkoxy and R_4 is selected from the group consisting of hydrogen or substituted or unsubstituted C_{1-4} alkoxy;

wherein a compound of formula (II) is added to a solvent, or a mixture of solvents, to form a reaction mixture, an oxidizing agent is added to said reaction mixture and said oxidation is

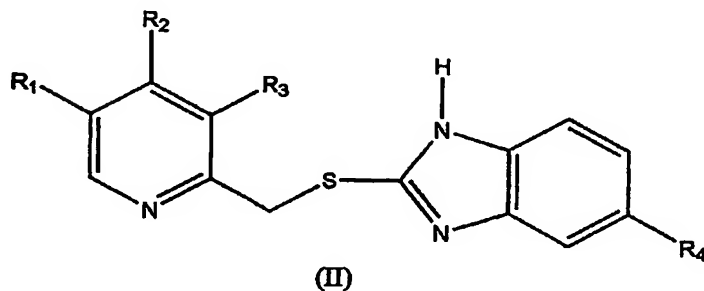
carried out at a controlled temperature and pH so as to prepare a compound of formula (I), and optionally converting a sulfinyl compound of formula (I) to a pharmaceutically acceptable salt, hydrate or solvate thereof,

characterised in that an alkali is present in the reaction mixture at least during said oxidation, whereby the pH of the reaction mixture at least during said oxidation is in the range of 9 to 12. Preferably the oxidizing agent comprises an aqueous hypohalite solution.

The present invention further provides a process for preparing a sulfinyl compound of formula (I), or a pharmaceutically acceptable salt, hydrate or solvate thereof,



which process comprises oxidation of a sulfide compound of formula (II)



wherein in both formulae (I) and (II) R₁ and R₃ are selected from the group consisting of hydrogen, methyl or C₁₋₄alkoxy, R₂ is selected from the group consisting of substituted or unsubstituted C₁₋₄alkoxy and R₄ is selected from the group consisting of hydrogen or substituted or unsubstituted C₁₋₄alkoxy;

characterised in that said compound of formula (II) is reacted with an oxidizing agent comprising an aqueous hypohalite solution, and optionally converting a sulfinyl compound of formula (I) to a suitable pharmaceutically acceptable salt, hydrate or solvate thereof.

Optionally, a compound of formula (II) is reacted with an aqueous hypohalite solution in the presence of a catalyst, suitably selected from the group consisting of pyridine, di-isopropyl ethyl amine and N,N-dimethyl amino pyridine. The use of such a catalyst is desirable to further avoid formation of undesirable by products.

Typically, a process according to the present invention comprises dissolving or suspending a sulphide precursor compound of formula (II) in a suitable solvent or mixture of solvents. Suitably, the solvent comprises water, lower alkyl alcohols, esters, ethers, chlorinated solvents, or mixtures thereof. A preferred solvent is selected from the group consisting of water, methanol, ethanol, isopropanol, di-isopropyl ether, dichloromethane, acetonitrile and ethyl acetate, or a mixture of two or more of these solvents. An aqueous hypohalite solution, preferably sodium hypochlorite, is then added slowly in a controlled manner at appropriate temperature conditions to give, after simple work up procedures, a sulfinyl compound of formula (I) in very high yield and purity.

A process according to the present invention is typically performed at a temperature in the range of -30 to 50°C. A preferred operating temperature is in the range of 0 to 30°C.

An aqueous hypohalite solution suitable for use in a process according to the present invention typically comprises an aqueous solution of an alkali metal or alkali earth metal hypohalite and is preferably selected from the group consisting of sodium hypochlorite, sodium hypobromite and calcium hypochlorite. Sodium hypochlorite is most preferred. An aqueous hypohalite solution suitable for use in a process according to the present invention typically has a concentration in the range of 2% to 30%. It is preferable, however, to use an aqueous hypohalite solution having a concentration in the range of 2% to 5%, for ease of handling.

The aqueous hypohalite solution is typically added to a reaction mixture comprising a sulphide precursor compound of formula (II) dissolved or suspended in a suitable solvent, or mixture of solvents, over a time period ranging from several minutes to several hours, depending on the strength of the hypohalite solution and the exothermicity of the reaction. It is preferable to perform the addition slowly over a period ranging from 30 minutes to 4 hours, with the time taken for completion of the reaction ranging from 2 to 10 hours.

A commercially available hypohalite solution can be employed, but it is advantageous to use a freshly prepared solution typically including about 0.5 % to 5 % of free corresponding alkali or alkali earth metal hydroxide. The presence of free alkali or alkali earth metal hydroxide not only stabilizes the hypohalite, but also exhibits an advantageous stabilising effect on the benzimidazole sulfinyl products which are known to be unstable in acidic conditions. Alternatively, a solution of an alkali or alkali earth metal hydroxide, or other suitable alkali, can be added to the suspension or solution of a precursor sulphide compound of formula (II) in the solvent, or mixture of solvents, before addition of the oxidizing agent.

A sulfinyl compound of formula (I) can be suitably isolated from the reaction mass by adjusting the pH using aqueous organic or inorganic acids. Typically, the pH is adjusted to be in the range of 6.0 to 9.5, more preferably in the range of 7 to 7.5, using aqueous acetic acid, followed by filtration to isolate a sulfinyl compound of formula (I).

A sulfinyl compound of formula (I) may be further purified by dissolving in a mixture of a C₁₋₄ alkanol, typically methanol, and an aqueous alkali metal hydroxide solution, typically sodium hydroxide solution. The pH of the resulting clear solution is adjusted to between 9.0 to 9.5, typically using aqueous ammonium acetate solution, and a sulfinyl compound of formula (I) is isolated by filtration.

Substantially as hereinbefore described a process according to the present invention can further comprise conversion of a sulfinyl compound of formula (I) to a suitable pharmaceutically acceptable salt, hydrate or solvate thereof, in particular a pharmaceutically acceptable salt form. Suitable salts include those with alkali or alkali earth metals, for example Mg²⁺, Ca²⁺, Na⁺, K⁺ or Li⁺ salts, in particular Mg²⁺ or Na⁺ salts.

In the case where R_2 represents substituted alkoxy substantially as hereinbefore described, suitable substituents include one or more halo substituents, such as one or more fluoro substituents, or one or more alkoxy substituents, such as C_{1-3} alkoxy, especially methoxy.

In the case where R_4 represents substituted alkoxy substantially as hereinbefore described, suitable substituents include one or more halo substituents, such as one or more fluoro substituents.

A preferred compound prepared according to a process of the present invention is lansoprazole, wherein in formula (I) R_1 represents methyl, R_2 represents trifluoroethoxy, R_3 represents hydrogen and R_4 represents hydrogen.

A further preferred compound prepared according to a process of the present invention is omeprazole, wherein in formula (I) R_1 represents methyl, R_2 represents methoxy, R_3 represents methyl and R_4 represents methoxy.

A further preferred compound prepared according to a process of the present invention is pantoprazole, wherein in formula (I) R_1 represents methoxy, R_2 represents methoxy, R_3 represents hydrogen and R_4 represents difluoromethoxy.

A further preferred compound prepared according to a process of the present invention is rabeprazole, wherein in formula (I) R_1 represents methyl, R_2 represents $OCH_2CH_2CH_2OMe$, R_3 represents hydrogen and R_4 represents hydrogen.

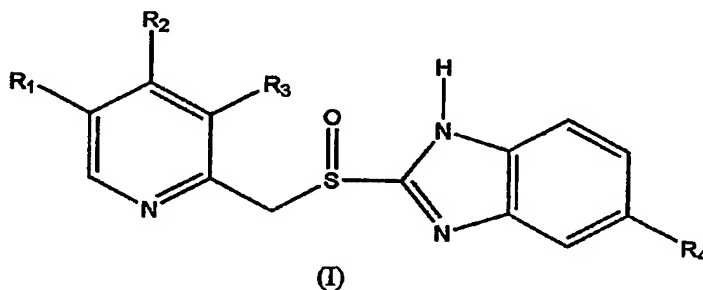
The present invention further provides lansoprazole prepared by a process substantially as hereinbefore described. Preferably lansoprazole thus provided by the present invention is substantially free of oxidation contamination by products.

The present invention further provides omeprazole prepared by a process substantially as hereinbefore described. Preferably omeprazole thus provided by the present invention is substantially free of oxidation contamination by products.

The present invention further provides pantoprazole prepared by a process substantially as hereinbefore described. Preferably pantoprazole thus provided by the present invention is substantially free of oxidation contamination by products.

The present invention further provides rabeprazole prepared by a process substantially as hereinbefore described. Preferably rabeprazole thus provided by the present invention is substantially free of oxidation contamination by products.

The present invention further provides a pharmaceutical composition comprising a sulfinyl compound of formula (I)



wherein R₁ and R₃ are selected from the group consisting of hydrogen, methyl or C₁₋₄alkoxy, R₂ is selected from the group consisting of substituted or unsubstituted C₁₋₄alkoxy and R₄ is selected from the group consisting of hydrogen or substituted or unsubstituted C₁₋₄alkoxy; which compound of formula (I) is prepared by a process substantially as hereinbefore described; together with a pharmaceutically acceptable carrier or excipient therefor. A preferred composition according to the present invention comprises lansoprazole prepared by a process substantially as hereinbefore described; together with a pharmaceutically acceptable carrier or excipient therefor. A further preferred composition according to the present invention comprises omeprazole prepared by a process substantially as hereinbefore described; together with a pharmaceutically acceptable carrier or excipient therefor. A further preferred composition according to the present invention comprises pantoprazole prepared by a process substantially as hereinbefore described; together with a pharmaceutically acceptable carrier or excipient therefor. A still further preferred

composition according to the present invention comprises rabeprazole prepared by a process substantially as hereinbefore described; together with a pharmaceutically acceptable carrier or excipient therefor.

There is further provided by the present invention, for use in therapy, lansoprazole prepared by a process substantially as hereinbefore described. There is also provided, for use in therapy, omeprazole prepared by a process substantially as hereinbefore described. There is also provided for use in therapy, pantoprazole prepared by a process substantially as hereinbefore described. There is still further provided for use in therapy, rabeprazole prepared by a process substantially as hereinbefore described.

The present invention also provides for use in the manufacture of a medicament for the treatment of gastric ulcers and related conditions, lansoprazole prepared by a process substantially as hereinbefore described. There is also provided for use in the manufacture of a medicament for the treatment of gastric ulcers and related conditions, omeprazole prepared by a process substantially as hereinbefore described. There is also provided for use in the manufacture of a medicament for the treatment of gastric ulcers and related conditions, pantoprazole prepared by a process substantially as hereinbefore described. There is still further provided for use in the manufacture of a medicament for the treatment of gastric ulcers and related conditions, rabeprazole prepared by a process substantially as hereinbefore described.

The present invention also provides a method of treating gastric ulcers and related conditions, which comprises administering to a patient in need of such treatment lansoprazole prepared by a process substantially as hereinbefore described. The present invention also provides a method of treating gastric ulcers and related conditions, which comprises administering to a patient in need of such treatment omeprazole prepared by a process substantially as hereinbefore described. The present invention also provides a method of treating gastric ulcers and related conditions, which comprises administering to a patient in need of such treatment pantoprazole prepared by a process substantially as hereinbefore described. The present invention also provides a method of treating gastric ulcers and related conditions,

which comprises administering to a patient in need of such treatment rabeprazole prepared by a process substantially as hereinbefore described.

The present invention is now further illustrated by the following examples, which do not in any way limit the scope of the invention. While the present invention is described above in connection with preferred or illustrative embodiments, these embodiments are not intended to be exhaustive or limiting of the invention. Rather, the invention is intended to cover all alternatives, modifications and equivalents included within its scope, as defined by the appended claims.

Examples

Example 1

Preparation of 2-[[[4-(3-methoxy-propoxy)-3-methyl-2-pyridinyl] methyl]-sulfinyl]-1H-benzimidazole sodium (rabeprazole sodium)

2-[[[4-(3-methoxy-propoxy)-3-methyl-2-pyridinyl]methyl]-thio]-1H-benzimidazole (10g) was suspended in 200ml of purified water, sodium hydroxide (about 2g) and pyridine (4ml). To this was slowly added about 75g of approximately 3.8% sodium hypochlorite solution in 2 hours. The reaction mass was maintained at 5 – 8° C for 4 hours. After completion of the reaction, excess sodium hypochlorite was decomposed using 5% aqueous sodium thiosulphate solution. The pH was adjusted to between 8.0 to 9.0 using 10% ammonium acetate solution.

After pH adjustment the compound was isolated from the water layer by adding ethyl acetate followed by extraction. Concentrating the organic layer under vacuum yielded a residue to which isopropyl acetate was added and stirred for about 1 hour, yielding the desired product. The product was purified by dissolving in a mixture of acetone and triethylamine. Rabeprazole base so obtained was dissolved in ethyl acetate and methanolic ammonia mixture to which methanolic sodium hydroxide was added and distilled off to a thick residue at low temperature. This was again redissolved in ethyl acetate and rabeprazole sodium salt was isolated in n-heptane / n-hexane and dried.

Example 2

Preparation of 5-(difluoromethoxy)-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl] sulfinyl]-1H-benzimidazole (pantoprazole)

5-(difluoromethoxy)-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]-thio]-1H-benzimidazole (10g) was dissolved in purified water (100ml) and methanol (10ml). 80g of 3.5% aqueous sodium hypochlorite solution having a sodium hydroxide content of up to 2.4 -2.8% was added to the reaction mass, which was maintained at 5 - 8° C for about 1 hour. Excess hypochlorite was

decomposed using 5% aqueous sodium thiosulphate solution. pH of the reaction mass was adjusted to 8.0 – 9.5 using ammonium acetate. The solids were filtered, washed with chilled water and dried in an oven to give 8.5g of the title compound.

Example 3

Preparation of (2-[[[3-methyl-4-(2,2,2-trifluoro-ethoxy)-2-pyridinyl]methyl]-sulfinyl]1H-benzimidazole (lansoprazole)

(2-[[[3-methyl-4-(2,2,2-trifluoro-ethoxy)-2-pyridinyl]methyl]-thio]1H-benzimidazole (10g) was suspended in 100ml of a mixture of acetonitrile and water (7:3). A solution of sodium hydroxide was added to this suspension. 61g of sodium hypochlorite solution (4.2%) was added over a period of 4 hours maintaining a temperature of 5°C – 10°C. Excess hypochlorite was decomposed using 3% aqueous sodium metabisulfite solution. Acetone (50ml) was added and the pH was adjusted to between 7.5 to 8.5 using dilute acetic acid. The solids were filtered, washed with chilled water and dried in an oven to give 8g of the title compound. The product was slurried in acetone followed by purification by dissolving in a mixture of acetone and aqueous sodium hydroxide solution. The pH of the clear solution was adjusted to about 7.0 – 8.0 using dilute acetic acid solution and the product was isolated by filtration, slurried in water and dried in an oven to give about 7g of the desired product.

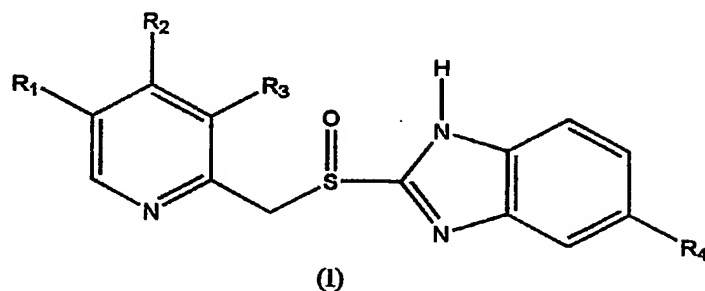
Example 4

Preparation of ((5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (omeprazole)

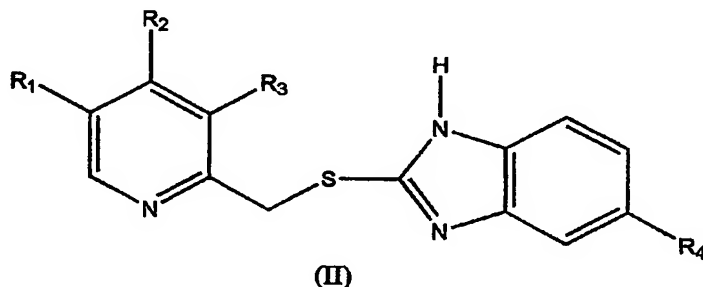
((5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridyl]methyl]-thio]-1H-benzimidazole, (20g) was suspended in 200ml of dichloromethane. 140g of sodium hypochlorite solution (chlorine content : 3.6 - 4.2%; sodium hydroxide content : 2.8 – 3.0 %) was added over a period of 3 hours maintaining a temperature of -5°C to 0°C. The organic layer was separated and extracted with 200ml of 5% sodium hydroxide solution. The pH of the aqueous layer was adjusted to between 8 - 8.5 using dilute acetic acid. The solids were filtered, washed with chilled water and dried in an oven to give 17g of the title compound.

CLAIMS

1. A process for preparing a sulfinyl compound of formula (I), or a pharmaceutically acceptable salt, hydrate or solvate thereof,



which process comprises oxidation of a sulfide compound of formula (II)

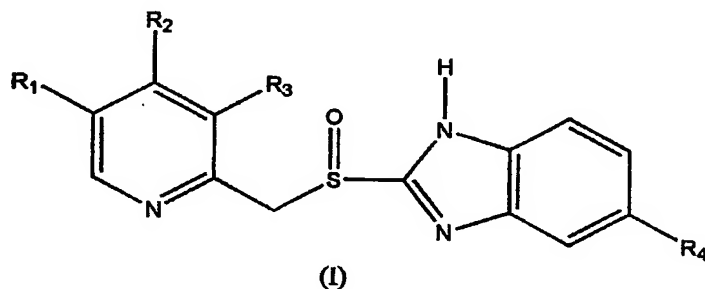


wherein in both formulae (I) and (II) R₁ and R₃ are selected from the group consisting of hydrogen, methyl or C₁₋₄alkoxy, R₂ is selected from the group consisting of substituted or unsubstituted C₁₋₄alkoxy and R₄ is selected from the group consisting of hydrogen or substituted or unsubstituted C₁₋₄alkoxy;

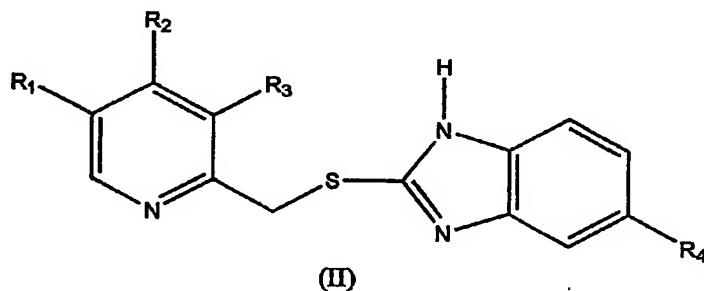
wherein a compound of formula (II) is added to a solvent, or a mixture of solvents, to form a reaction mixture, an oxidizing agent is added to said reaction mixture and said oxidation is carried out at a controlled temperature and pH so as to prepare a compound of formula (I), and optionally converting a sulfinyl compound of formula (I) to a pharmaceutically acceptable salt, hydrate or solvate thereof,

characterised in that an alkali is present in the reaction mixture at least during said oxidation, whereby the pH of the reaction mixture at least during said oxidation is in the range of 9 to 12.

2. A process according to claim 1, wherein said oxidizing agent comprises an aqueous hypohalite solution.
3. A process for preparing a sulfinyl compound of formula (I), or a pharmaceutically acceptable salt, hydrate or solvate thereof,



which process comprises oxidation of a sulfide compound of formula (II)



wherein in both formulae (I) and (II) R₁ and R₃ are selected from the group consisting of hydrogen, methyl or C₁₋₄alkoxy, R₂ is selected from the group consisting of substituted or unsubstituted C₁₋₄alkoxy and R₄ is selected from the group consisting of hydrogen or substituted or unsubstituted C₁₋₄alkoxy;

characterised in that said compound of formula (II) is reacted with an oxidizing agent comprising an aqueous hypohalite solution, and optionally converting a sulfinyl compound of formula (I) to a pharmaceutically acceptable salt, hydrate or solvate thereof.

4. A process according to claim 2 or 3, wherein a compound of formula (II) is reacted with an aqueous hypohalite solution optionally in the presence of a catalyst selected from the group consisting of pyridine, di-isopropyl ethyl amine and N,N-dimethyl amino pyridine.

5. A process according to any of claims 1 to 4, which comprises or further comprises dissolving or suspending a compound of formula (II) in a solvent selected from the group consisting of water, lower alkyl alcohols, esters, ethers and chlorinated solvents, or a mixture of two or more of these solvents.

6. A process according to claim 5, wherein said solvent is selected from the group consisting of water, methanol, ethanol, isopropanol, di-isopropyl ether, dichloromethane, acetonitrile and ethyl acetate, or a mixture of two or more of these solvents.

7. A process according to any of claims 1 to 6, which is carried out at a temperature in the range of -30 to 50°C.

8. A process according to claim 7, which is carried out at a temperature in the range of 0 to 30°C.

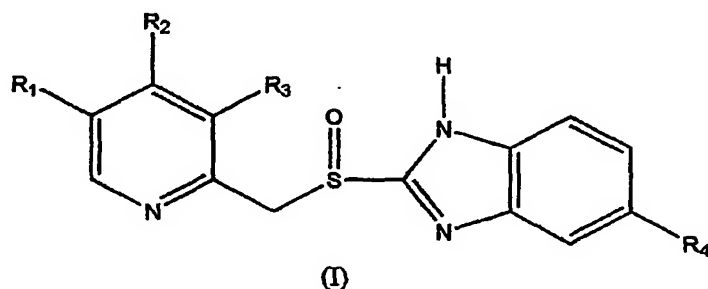
9. A process according to any of claims 2 to 8, wherein said aqueous hypohalite solution comprises an aqueous solution of an alkali metal or alkali earth metal hypohalite.

10. A process according to claim 9, wherein said alkali metal or alkali earth metal hypohalite is selected from the group consisting of sodium hypochlorite, sodium hypobromite and calcium hypochlorite.

11. A process according to claim 10, wherein said aqueous hypohalite solution comprises sodium hypochlorite.

12. A process according to any of claims 2 to 11, wherein said aqueous hypohalite solution has a concentration in the range of 2% to 30%.
13. A process according to claim 12, wherein said aqueous hypohalite solution has a concentration in the range of 2% to 5%.
14. A process according to any of claims 2 to 13, wherein said aqueous hypohalite solution includes about 0.5 % to 5 % of free corresponding alkali or alkali earth metal hydroxide, whereby a pH in the range of 9 to 12 is obtained for a reaction mixture comprising a compound of formula (II), and a solvent, or a mixture of solvents, at least during said oxidation.
15. A process according to any of claims 1 to 13, wherein an alkali is added to a reaction mixture comprising a compound of formula (II), and a solvent, or a mixture of solvents, prior to addition of said oxidizing agent to the reaction mixture, whereby a pH in the range of 9 to 12 is obtained for said reaction mixture at least during said oxidation.
16. A process according to any of claims 1 to 15, wherein in formula (I) R_1 represents methyl, R_2 represents trifluoroethoxy, R_3 represents hydrogen and R_4 represents hydrogen.
17. A process according to any of claims 1 to 15, wherein in formula (I) R_1 represents methyl, R_2 represents methoxy, R_3 represents methyl and R_4 represents methoxy.
18. A process according to any of claims 1 to 15, wherein in formula (I) R_1 represents methoxy, R_2 represents methoxy, R_3 represents hydrogen and R_4 represents difluoromethoxy.
19. A process according to any of claims 1 to 15, wherein in formula (I) R_1 represents methyl, R_2 represents $OCH_2CH_2CH_2OMe$, R_3 represents hydrogen and R_4 represents hydrogen.

20. Lansoprazole prepared according to claim 16, substantially free of oxidation contamination by products.
21. Omeprazole prepared according to claim 17, substantially free of oxidation contamination by products.
22. Pantoprazole prepared according to claim 18, substantially free of oxidation contamination by products.
23. Rabeprazole prepared according to claim 19, substantially free of oxidation contamination by products.
24. A pharmaceutical composition comprising a sulfinyl compound of formula (I)



wherein R₁ and R₃ are selected from the group consisting of hydrogen, methyl or C₁₋₄alkoxy, R₂ is selected from the group consisting of substituted or unsubstituted C₁₋₄alkoxy and R₄ is selected from the group consisting of hydrogen or substituted or unsubstituted C₁₋₄alkoxy;

prepared according to any of claims 1 to 19, together with a pharmaceutically acceptable carrier or excipient therefor.

25. A pharmaceutical composition comprising lansoprazole according to claim 20, together with a pharmaceutically acceptable carrier or excipient therefor.

26. A pharmaceutical composition comprising omeprazole according to claim 21, together with a pharmaceutically acceptable carrier or excipient therefor.
27. A pharmaceutical composition comprising pantoprazole according to claim 22, together with a pharmaceutically acceptable carrier or excipient therefor.
28. A pharmaceutical composition comprising rabeprazole according to claim 23, together with a pharmaceutically acceptable carrier or excipient therefor.
29. For use in therapy, lansoprazole according to claim 20.
30. For use in therapy, omeprazole according to claim 21.
31. For use in therapy, pantoprazole according to claim 22.
32. For use in therapy, rabeprazole according to claim 23.
33. For use in the manufacture of a medicament for the treatment of gastric ulcers and related conditions, lansoprazole according to claim 20.
34. For use in the manufacture of a medicament for the treatment of gastric ulcers and related conditions, omeprazole according to claim 21.
35. For use in the manufacture of a medicament for the treatment of gastric ulcers and related conditions, pantoprazole according to claim 22.
36. For use in the manufacture of a medicament for the treatment of gastric ulcers and related conditions, rabeprazole according to claim 23.
37. A method of treating gastric ulcers and related conditions, which comprises administering to a patient in need of such treatment lansoprazole according to claim 20.

38. A method of treating gastric ulcers and related conditions, which comprises administering to a patient in need of such treatment omeprazole according to claim 21.
39. A method of treating gastric ulcers and related conditions, which comprises administering to a patient in need of such treatment pantoprazole according to claim 22.
40. A method of treating gastric ulcers and related conditions, which comprises administering to a patient in need of such treatment rabeprazole according to claim 23.

INTERNATIONAL SEARCH REPORT

PCT/GB 20/04000064

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D401/12 A61K31/4439 A61P1/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 017 560 A (HIRAI SHIN-ICHIRO ET AL) 25 January 2000 (2000-01-25) column 4, line 11 - line 16	3-19
X	US 5 708 013 A (SHIMOMURA NAUYUKI ET AL) 13 January 1998 (1998-01-13) column 4 -column 5; example 5	1,2,4-19
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *S* document member of the same patent family

Date of the actual completion of the international search

24 March 2004

Date of mailing of the international search report

27/05/2004

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INTERNATIONAL SEARCH REPORT

PCT/GB 20/0400006

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 2 134 523 A (HAESSE AB) 15 August 1984 (1984-08-15) cited in the application page 19, line 1 - line 15 -----	1,2,4-19
X	VYAS K ET AL: "LANSOPRAZOLE, AN ANTIULCERATIVE DRUG" ACTA CRYSTALLOGRAPHICA SECTION C. CRYSTAL STRUCTURE COMMUNICATIONS, MUNKSGAARD, COPENHAGEN, DK, vol. C56, no. 12, 2000, pages E572-E573, XP009014904 ISSN: 0108-2701 the whole document -----	20-40
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X	WILLIAMS M P ET AL: "Review article: the pharmacology of rabeprazole" ALIMENTARY PHARMACOLOGY & THERAPEUTICS, BLACKWELL SCIENTIFIC PUBLICATIONS LTD., CAMBRIDGE, GB, vol. 13, no. 3, 1999, pages 3-10, XP002963613 ISSN: 0269-2813 the whole document -----	20-40
X	GARNER A ET AL: "PANTOPRAZOLE: A NEW AND MORE SPECIFIC PROTON PUMP INHIBITOR" EXPERT OPINION ON INVESTIGATIONAL DRUGS, ASHLEY PUBLICATIONS LTD., LONDON, GB, vol. 6, no. 7, 1997, pages 885-893, XP009025982 ISSN: 1354-3784 the whole document -----	20-40

INTERNATIONAL SEARCH REPORT

PCT/GB 20/04000064

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 37-40 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

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PCT/GB 20/04000064

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